REMARKS

I. Objection to the Specification

The Examiner has identified sequences on page 36, lines 21-22 of the specification that are not labeled with SEQ ID NOs (Office Action, page 2). Applicants submit that the three sequences on lines 21-22 do not require SEQ IDs and that no updated sequence listing is required. Under 37 CFR 1.821 only sequences with 4 or more "specifically defined" amino acids need to be listed in a sequence listing (See, also MPEP 2421.02). According to 37 CFR 1.821, "specifically defined" means "those amino acids other than 'Xaa'" (where "Xaa" means unknown or other, see MPEP 2422, Table 3). The three sequences pointed to by the Examiner have, at most, three specific amino acids, with the remainder being non-defined "X" amino acids. As such, since only three (or two) specific amino acids are contained in these sequences, Applicants submit that no SEQ IDs, or updated sequence listing, are required.

II. The 112 Rejection Should Be Withdrawn

The Examiner has rejected the claims as allegedly lacking written description, arguing that the Specification provides insufficient support for the scope of the claims. Applicants respectfully disagree.

Initially, it is noted that the present claims are copied from U.S. Pat. No. 5,939,301 ("the '301" patent). In issuing the '301 patent, the Patent Office has taken the position that the disclosure of the '301 patent was sufficient to support its issued claims, which are the same claims of the present invention. Yet the present specification provides substantially more support for the claims than does the '301 patent (see below). Thus, the specification of the present invention must also provide sufficient support for the claims. To hold otherwise, the Examiner must take the position that the '301 patent claims were improperly issued and are not valid. If this is the case, Applicants encourage the Examiner to initiate a re-examination of the '301 patent.

Claim 40 of the present application is a verbatim copy of claim 29 of the '301 patent.

40. A mutant Thermotoga neapolitana DNA polymerase having a mutation that substantially reduces or eliminates 3'-5' exonuclease activity of said polymerase, wherein said mutation is in the 3'-5' exonuclease domain of said polymerase, and further wherein said mutant Thermotoga neapolitana DNA polymerase is a Pol I-type DNA polymerase.

29. A mutant Thermotoga neapolitana DNA polymerase having a mutation that substantially reduces or eliminates 3'-5' exonuclease activity of said polymerase, wherein said mutation is in the 3'-5' exonuclease domain of said polymerase, and further wherein said mutant Thermotoga neapolitana DNA polymerase is a Pol I-type DNA polymerase.

Likewise, Claim 44 of the present application is a verbatim copy of claim 34 of the '301 patent.

44. A mutant Thermotoga neapolitana DNA polymerase having a mutation that substantially reduces or eliminates 5'-3' exonuclease activity of said polymerase, wherein said mutation is in the 5'-3' exonuclease domain of said polymerase, and further wherein said mutant Thermotoga neapolitana DNA polymerase is a Pol I-type DNA polymerase.

34. A mutant Thermotoga neapolitana DNA polymerase having a mutation that substantially reduces or eliminates 5'-3' exonuclease activity of said polymerase, wherein said mutation is in the 5'-3' exonuclease domain of said polymerase, and further wherein said mutant Thermotoga neapolitana DNA polymerase is a Pol I-type DNA polymerase.

Importantly, the specification of the present invention provides detailed guidance demonstrating that the inventors were in possession of the claimed invention. As highlighted in Applicants previous response, the present specification provides detail of the structure/function relationship between the structure of the polymerase and its enzymatic activities—in line with the instruction provided by the Revised Interim Written Description Guidelines for allowable claims:

1) Numerous illustrative examples of specific non-naturally-occurring *Thermotoga neapolitana* DNA polymerases. (Note--some of these mutants are specifically claimed in dependent claims, such as original claim 30 and new claims 48 and 49.

The specification demonstrates reduction to practice of these mutants. Therefore, the rejection must be withdrawn at least with respect to these dependent claims).

2) Substantial guidance for selection of numerous addition non-natural *Thermotoga neapolitana* DNA polymerases based on homologies to other characterized polymerases as shown in the Figures 1-4 of the specification.

3) Identification of specific zones that can be mutated to yield enzymes with the desired activities and properties.

Nothing more should be needed. Had Applicants generated 100, 1000, or more specific examples (which can readily be done per the teachings of the specification), this would only serve to illustrate the invention in the same manner in which it is currently illustrated.

Applicants previously requested that the Examiner provide evidence (as required by law to sustain the rejection) to support the position that Applicants guidance is insufficient to support the claim scope. In the latest office action, the Examiner has not provided any evidence to support the rejection: only arguments and unsupported conclusory statements are provided. The Office has the burden of presenting evidence to support its position (See MPEP 2163.04, and the Written Description Guidelines). Notably, in the 103 rejection, the Examiner cites the Erlich reference in a manner that directly contradicts the Examiner's position in the written description rejection (citing Erlich for the proposition that, with the *Thermotoga neapolitana* DNA polymerase sequence and prior art knowledge, a variety of variant sequences are readily knowable). Thus, the only evidence cited by the Examiner relevant to the written description issue supports the allowability of the Applicants claims. Applicants need not have provided any of the above evidence to counter the rejection—as a *prima facie* showing was not made by the Examiner in the first instance. In view of the evidence provided by the Applicants and the complete lack of evidence provided by the Office, the rejections must be withdrawn.

In particular, the Examiner maintains the rejection by arguing that the claims encompass any and all mutants of any DNA polymerase (any pol-I, -II or –III type of polymerase) or fragments thereof capable of DNA synthetic activity which is derived from *Thermotoga neapolitana* (Applicants note that, as amended, all claims recite that the claimed polymerase is the pol-I type polymerase from *Thermotoga neapolitana*). The Examiner has provided no evidence to suggest that Applicants description of the pol-I type polymerase from *Thermotoga neapolitana* (which includes the identification of the polymerase domain and other domains that can be altered without impacting the polymerase domain) is insufficient to show possession of a broad genus of mutant pol-I type polymerases from *Thermotoga neapolitana.*

The Written Description Guidelines provide numerous biotechnology examples to highlight allowable subject matter and non-allowable subject matter. The Guidelines explain that non-allowable claims typically arise where the structure of the gene or protein is not known or only partially known or where there is no understanding of the structure/function relationship of the gene or protein structure with its function (see e.g., Example 17 of the Written Description Guidelines, where structure/function relationship is not known). None of these examples apply in the present case. Here, the full structure is provided and the regions of the structure that relate to the various activities of the enzyme are described. Numerous specific examples of mutants in these regions are described to illustrate the claimed mutant polymerases. Applicants point the Examiner to Example 14 of the Written Description Guidelines that illustrates an allowable protein claim defined by an enzymatic activity (similar to the present claims). The primary difference between the present case and Example 14 of the Written Description Guidelines is that the present case provides more support than the allowable subject matter of Example 14. In particular, Example 14 of the Written Description Guidelines does not provide any specific variant sequences that illustrate the protein having the claimed activity. In the present case, numerous such examples are provided. Thus, per the Written Description Guidelines, the present claims fall squarely within the range of allowable subject matter.

To sustain the rejection, the Examiner must provided evidence (via reference, affidavit, or other concrete source) that Applicant's examples and structure/function

characterization are insufficient to show possession of the invention for the claimed polymerases. Such evidence must be specific to the nature of the claimed polymerase. Without such evidence, the claims must be allowed. Argument and unsupported conclusory statements are legally insufficient.

III. The Invention is Novel

Claims 22 and 23 stand rejected as allegedly being anticipated by Chatterjee et al. (U.S. Pat. No. 5,912,155; hereinafter, the '155 patent) and Claims 22-30, 40 and 44 stand rejected as allegedly being obvious in view of the '155 patent and Erlich et al. Applicants respectfully disagree.

It is noted that only Claims 22 and 23 are rejected as lacking novelty. Thus, the remaining claims are allowable if the obviousness rejection is withdrawn. A careful review of Chatterjee demonstrates that the obviousness rejection must be withdrawn. First, it is noted that Chatterjee only provides a very limited and partial sequence of the *Thermotoga neapolitana* polymerase. Therefore, Chatterjee, in combination with any other polymerase reference, cannot provide an expectation of success that mutants can be generated that maintain or remove the desired enzymatic activities. The Chatterjee patent guesses that particular mutants might be made. A guess does not provide an expectation of success. This is particularly clear in the present case because Chatterjee **guessed wrong**. A primary basis of the Examiner's rejection is that Chatterjee's description of deleting the 3'-5' exonuclease domain provides support for mutants lacking 3'-5' exonuclease activity. However, Chatterjee does not provide the full sequence of the 3'-5' exonuclease domain. Furthermore, as shown in Applicant's specification, deletion of the 3'-5' exonuclease domain of *Thermotoga neapolitana* destroys polymerase activity (see data related to pJM284ΔB). Thus, Chatterjee's prediction that the region could be deleted (keeping in mind that Chatterjee does not provide the full sequence of the region in the first place), while maintaining polymerase activity, is wrong and demonstrates that Chatterjee is not enabling for mutant polymerases as Chatterjee did not: 1) have the sequence of *Thermotoga neapolitana*; and 2) demonstrate any mutant sequences.

There can be no stronger evidence of a lack of expectation of success—that Chatterjee's contemplated embodiments, in fact, fail. The Specification of the present

invention obtains 3'-5' exonuclease deficient mutants by modifying amino acids with the 3'-5' exonuclease domain (which Applicants, unlike Chatterjee, provide the full sequence of) rather than by deletion. Thus, the combination of Chatterjee with Erlich fails to teach or suggest the presently claimed invention and claims 24-30, 40, 44, 48, and 49 should be passed to allowance. Furthermore, for the reasons discussed below, the '155 patent may not be used as prior art against the present application.

With respect to the novelty rejection of claims 22 and 23, Applicants submit herewith a Statement under CFR 1.608(b) with supporting Declarations demonstrating that Applicant is *prima facie* entitled to a judgment relative to the patentee.

In particular, based on the file history of the '155 patent, it is clear that Chatterjee did not have the sequence of the *Thermotoga neapolitana* polymerase prior to September 30, 1994, as the priority application filed September 30, 1994 does not provide any sequence information. The September 30, 1994 reference also provides no description of mutants or non-natural *Thermotoga neapolitana* polymerase sequences. The September 30, 1994 filing has an incorrect restriction map of the *Thermotoga neapolitana* polymerase, indicating that even the earliest characterizations of the *Thermotoga neapolitana* polymerase by Chatterjee were wrong.

The specification that led to the '155 Chatterjee patent was filed January 9, 1995. This specification provided the first sequence information and only a partial sequence of the *Thermotoga neapolitana* polymerase corresponding to the N-terminal region. A paragraph was added to the specification referring to a deletion mutant in the 3'-5' exonuclease domain. However, the sequence of the 3'-5' exonuclease domain was not provided in the specification and the prophetic deletion mutant contemplated in the patent does not work—i.e., the prophetic description was wrong.

Thus, it is clear that, as of January 9, 1995, Chatterjee only had partial sequence information and had incorrectly predicted non-natural sequences. As of September 30, 1994, no sequence was provided and no reference to or suggestion of non-natural *Thermotoga neapolitana* polymerase sequences was provided.

The first correct mutant sequences disclosed by Chatterjee were on October 2, 1995, in the filing of U.S. Pat. No. 5,939,301, which is after the filing date of the Applicant's application and after public disclosure of Applicant's invention—a public

disclosure that was viewed by scientists from Life Technologies, the assignee of the '301 patent. The '301 patent disclosed additional sequence of the *Thermotoga neapolitana* polymerase, but still does not provide the full sequence.

As demonstrated by the Declaration of James Hartnett,[1] Applicant conceived of and reduced to practice the claimed invention prior to the filing date of '155 patent. Applicant had obtained the full sequence of the *Thermotoga neapolitana* polymerase and generated 5' exonuclease mutants prior to the September 30, 1994 date. Applicant also generated 3'-5' exonuclease mutants prior to the filing date of the '155 patent.

Thus, the evidence unequivocally demonstrates that Applicant had:

1) obtained the sequence of the *Thermotoga neapolitana* polymerase prior to Chatterjee; and

2) conceived of and reduced to practice non-natural *Thermotoga neapolitana* polymerase prior to Chatterjee; including 5' exonuclease and 3'-5' exonuclease activity variants.

In the alternative, Chatterjee was in possession of such data, but chose to suppress or conceal the data from specification of the September 30, 1994 and January 9, 1995 patent application filings. In either case, Applicant is entitled to a judgment relative to the patentee.

[1] Mr. Hartnett was not available to sign the declaration at the time of filing of this response. A signature copy will follow. Applicants note that the content of the Declaration is the same as a Declaration filed and signed by Mr. Hartnett under 37 C.F.R. 1.131 in Applicant's previous response.

CONCLUSION

All grounds of rejection of the Office Action of August 12, 2003 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 8/5/04

Jason R. Bond
Registration No. 45,439

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105

PATENT
Attorney Docket No. **PRMG 04578**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Slater, et al.	Group No.:	1652
Serial No.:	09/641,319	Examiner:	R. Hutson
Filed:	08/18/2000		
Entitled:	**Thermophilic DNA Polymerases From Thermotoga Neapolitana**		

STATEMENT UNDER 37 CFR 1.608(b)

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

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Dated: 8-5-04 By: _____

Examiner Hutson:

I, David Casimir, hereby declare and state, under penalty of perjury, that:

1. I am an attorney of record for this invention.

2. On information, evidence, and belief, as demonstrated by the evidence discussed below, Applicant is *prima facie* entitled to a judgment relative to the patentee.

3. In particular, based on the file history of U.S. Pat. No. 5,912,155 (hereinafter, "the '155 patent"), it is clear that the inventors of the '155 patent did not have the sequence of the *Thermotoga neapolitana* polymerase prior to September 30, 1994, as the priority application filed September 30, 1994 (attached hereto at Tab A) does not provide any sequence information (Declaration of Michael Slater in Support of Statement Under 1.608(b)). The September 30, 1994 reference also provides no description of mutants or non-natural *Thermotoga neapolitana* polymerase sequences (Declaration of Michael Slater in Support of Statement Under 1.608(b)). The September 30, 1994 filing has an incorrect restriction map of the *Thermotoga neapolitana*

polymerase , indicating that even the earliest characterizations of the *Thermotoga neapolitana* polymerase by Chatterjee were wrong (Declaration of Michael Slater in Support of Statement Under 1.608(b)).

4. The specification that led to the '155 Chatterjee patent was filed January 9, 1995 (attached hereto at Tab B). This specification provided the first sequence information and only a partial sequence of the *Thermotoga neapolitana* polymerase corresponding to the N-terminal region (Declaration of Michael Slater in Support of Statement Under 1.608(b)). A paragraph was added to the specification referring to a deletion mutant in the 3'-5' exonuclease domain. However, the sequence of the 3'-5' exonuclease domain was not provided in the specification and the prophetic deletion mutant contemplated in the patent does not work—i.e., the prophetic description was wrong (Declaration of Michael Slater in Support of Statement Under 1.608(b)).

5. Thus, it is clear that, as of January 9, 1995, Chatterjee only had partial sequence information and had incorrectly predicted non-natural sequences (Declaration of Michael Slater in Support of Statement Under 1.608(b)). As of September 30, 1994, no sequence was provided and no reference to or suggestion of non-natural *Thermotoga neapolitana* polymerase sequences was provided (Declaration of Michael Slater in Support of Statement Under 1.608(b)).

6. The first correct mutant sequences disclosed by Chatterjee were on October 2, 1995, in the filing of U.S. Pat. No. 5,939,301, which is after the filing date of the Applicant's application and after public disclosure of Applicant's invention—a public disclosure that was viewed by scientists from Life Technologies, the assignee of the '301 patent (Declaration of Michael Slater in Support of Statement Under 1.608(b)). The '301 patent disclosed additional sequence of the *Thermotoga neapolitana* polymerase, but still does not provide the full sequence (Declaration of Michael Slater in Support of Statement Under 1.608(b)).

7. Applicant conceived of and reduced to practice the claimed invention prior to the filing date of '155 patent (Declaration of James Hartnett in Support of Statement Under 1.608(b)). Applicant had obtained the full sequence of the *Thermotoga neapolitana* polymerase and generated 5' exonuclease mutants prior to the September 30, 1994 date (Declaration of James Hartnett in Support of Statement Under 1.608(b)). Applicant also generated 3'-5' exonuclease mutants prior to the filing date of the '155 patent (Declaration of James Hartnett in Support of Statement Under 1.608(b)).

8. Thus, the evidence unequivocally demonstrates that Applicant had:

1) obtained the sequence of the *Thermotoga neapolitana* polymerase prior to Chatterjee; and

2) conceived of and reduced to practice non-natural *Thermotoga neapolitana* polymerase prior to Chatterjee; including 5' exonuclease and 3'-5' exonuclease activity variants.

In the alternative, Chatterjee was in possession of such data, but chose to suppress or conceal the data from specification of the September 30, 1994 and January 9, 1995 patent application filings. In either case, Applicant is entitled to a judgment relative to the patentee.

9. I further declare that all statements made herein are of my own knowledge, are true, and that all statements are made on information and belief that are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application of any patent issued thereon.

Dated: 8/4/04

David Casimir

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Slater, et al.	Group No.:	1652
Serial No.:	09/641,319	Examiner:	R. Hutson
Filed:	08/18/2000		
Entitled:	**Thermophilic DNA Polymerases From Thermotoga Neapolitana**		

DECLARATION OF JAMES HARTNETT IN SUPPORT OF 37 CFR 1.608(b) STATEMENT

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CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

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Dated: 8-5-04 By: Michelle Wade

Examiner Hutson:

I, James Hartnett, hereby declare and state, under penalty of perjury, that:

1. I am one of the inventors of the above-named patent application (hereinafter "present application").

2. The claimed invention was reduced to practice in the United States of America prior to January 9, 1995, as indicated from this Declaration and the attached notebook pages. The work presented in the notebook pages was performed in this country by me or under my supervision. As evidenced from these documents, we developed mutant DNA polymerases derived from *Thermotoga neapolitana*. This includes mutants shown in Figure 4 of the present application. For example, the deletion mutant *Thermotoga neapolitana* polymerase labeled as M284, which provides a reduction in 5'-3' exonuclease activity through generation of a deletion

mutation is described on pages 31 (design) and 50 (activity assay of generated mutant) of the notebook 100893. This work was completed prior to September 30, 1994. Likewise, substitution mutants that reduce 3'-5' exonuclease activity were generated. For example, the combination deletion and substitution mutant *Thermotoga neapolitana* polymerase labeled as M284 (D323A, D389A) in Figure 4 of the present application is described on pages 27 (design) and 54 (use of the mutant enzyme in sequencing reaction) of notebook 100996 (the D323A is referred to as D355A and D389A is referred to as D424A in the notebook). This work was completed prior to January 9, 1995.

3. I further declare that all statements made herein are of my own knowledge, are true, and that all statements are made on information and belief that are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application of any patent issued thereon.

Dated: _____

_____

James Hartnett

To remove the 5'→3' exo activity of Tne, one course of action will be to digest the gene at Met 284 with BspHI and ligate that to the NcoI site of pALTERex1. This removes 283 AA's from the N-terminal end. The BspHI site is not unique so I had to do some monkeying around.

Digest 1

10µl pGTne 1
2µl XbaI
2µl NdeI
Buffer D

4.2kb fragment removed and purified with Wizard DNA clean-up.

Digest 2

25µl	4.2kb fragment		17µl	4.2kb fragment
3µl	BspHI NEB		2µl	KpnI
2µl	KpnI		5µl	Buffer J
5µl	Buffer (4) NEB			

All fragments seen are of the expected size.
The 1050 bp BspHI – KpnI pol fragment
1300 bp KpnI – XbaI pol fragment
5846 bp NcoI – XbaI vector

were co-isolated with Wizard and ligated in a 50µl volume.

Continued on Page 34

Read and Understood By

Jim Hartett
Signed

REDACTED
Date

Claire Schenbo
Signed

REDACTED
Date

PROJECT 5'→3' exo assay

Notebook No. 49

Continued From Page

The 5'→3' exo assay consists of incubating two 32P labeled substrate with 5u of enzyme for one hour at 74°C and then looking for 32P release off the substrates. Reactions done in duplicate. Release measured by DE81 binding.

Results

We expected Taq and Tne (native) demonstrate a 5'→3' exo activity, whereas UlTma and M284 Tne do not. I don't feel that the 2.7% release from M284 is significant since only one of the two duplicates is showing release.

SAMPLE		CPM1	
Ø (NO WASH)	1	3880.00	
	2	3978.00	
Ø	3	4016.00	
	4	3966.00	7% release
Taq	5	3808.00	
	6	3582.00	7.4%
UlTma	7	4076.00	
	8	3842.00	0%
Tne	9	3478.00	
	10	3552.00	11.9%
M284	11	3998.00	
	12	3768.00	2.7%
	13	3888.00	
	14	4012.00	
Ø	15	3758.00	
	16	3948.00	7% release
Taq	17	1170.00	
	18	1132.00	70%
UlTma	19	4060.00	
	20	4044.00	0%
Tne	21	2770.00	
	22	2738.00	28%
M284	23	4074.00	
	24	3992.00	0%

Continued on Page 51

Read and Understood By

Signed

Date

REDACTED

Signed

Date

REDACTED

To be sure 3'→5' exo activity is completely removed I want to have a D355A, D424A double mutant. This is accomplished by ~~transferring~~ exchanging the 215 bp. Csp45I fragment of D355A into the D424A background.

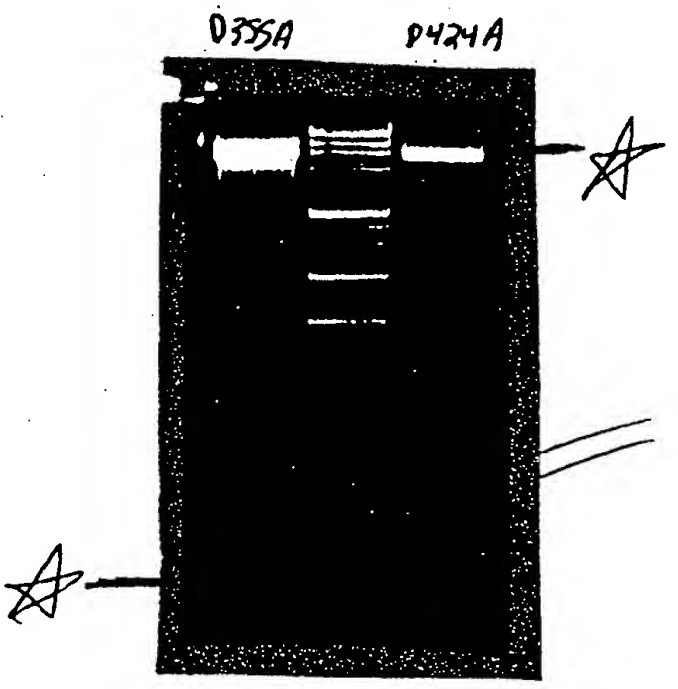
4 µg D355A plasmid cut with Csp45I
1 µg D424A plasmid cut with Csp45I

D424A reaction phosphatased
run on 1.5% TAE gel
indicated bands co-isolated with Wizard
Ligated in 40 µl volume overnight at 16°C

10-18-94 Ligations transformed into JM109

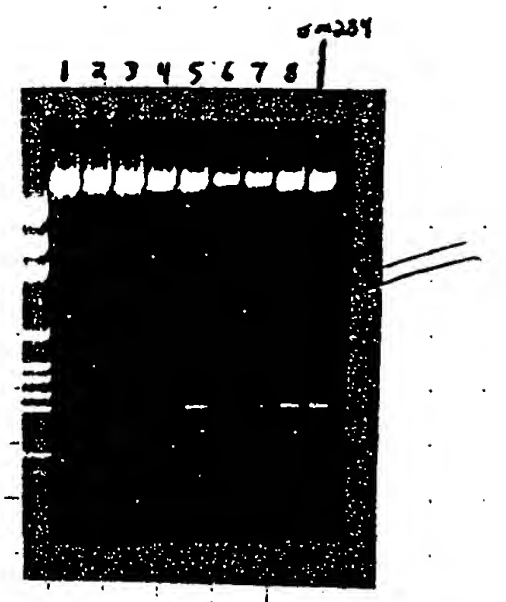
10-19-94 8 colonies streaked out

10-20-94 8 mini preps done and cut with BglII



Results

⑤, ⑥, ⑦, ⑧ show the expected 348bp BglII fragment, although ⑥ seems to have an extra band.



Continued on Page 28

Read and Understood By

Jim Hartsell — Signed — REDACTED — Date

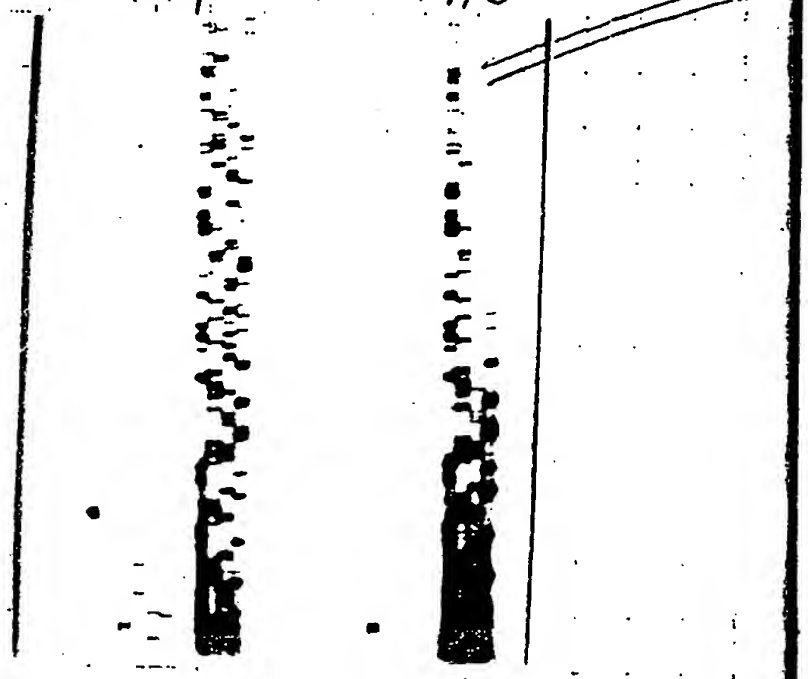
Elaine Ackerman — Signed — REDACTED — Date

I used the following ddNTPs
Template was Tne mutant 75-5A1 and
primer was JH66. 70°↔95°.

G = 30 μM
A = 75 μM
T = 75 μM
C = 30 μM

Results

Tne doesn't look much better.
Taq looks very unbalanced.
I need to repeat this + try
lower ddNTPs for A, T, + C.



Continued on Page 56

Read and Understood By

Signed

Date

Signed

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Slater, et al.	Group No.:	1652
Serial No.:	09/641,319	Examiner:	R. Hutson
Filed:	08/18/2000		
Entitled:	**Thermophilic DNA Polymerases From Thermotoga Neapolitana**		

DECLARATION OF MICHAEL SLATER IN SUPPORT OF 37 CFR 1.608(b) STATEMENT

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Dated: 8-5-04 By: _____

Examiner Hutson:

I, Michael Slater, hereby declare and state, under penalty of perjury, that:

1. I am one of the inventors of the above-named patent application (hereinafter "present application").

2. I have reviewed the '155 patent to Chatterjee as well as the priority document filed September 30, 1994. Based on the disclosures of these documents, it is clear that my research group conceived of and reduced to practice non-natural *Thermotoga neapolitana* polymerase prior to the inventors of the '155 patent, including non-natural *Thermotoga neapolitana* polymerases having mutations that alter 5' exonuclease activity and 3'-5' exonuclease activity. The priority documents filed September 30, 1994 does not contain any *Thermotoga neapolitana* polymerase sequence information. This lack of sequence information prevents a scientist from

identifying regions of the polymerase that correspond to the various enzymatic activities of the polymerase, prevents sequence alignments to other known polymerases, and prevents design of mutants of the sequence. The priority document filed September 30, 1994 makes no mention of non-natural *Thermotoga neapolitana* polymerases. Furthermore, one of the few characterizations of the natural *Thermotoga neapolitana* polymerase described in the September 30, 1994, a restriction enzyme digest map, is wrong as evidenced by the later correction of the restriction map in the January 5, 1995 patent application filing. The January 5, 1995 patent application filing provides only a limited, partial sequence of the *Thermotoga neapolitana* polymerase near the N-terminal end of the *Thermotoga neapolitana* polymerase. The sequence provided does not include the full sequence for the 3'-5' exonuclease domain. The specification provides a description of a 3'-5' exonuclease domain deletion mutant. However, the specification does not provide data showing that such a mutant was made. From my own experimental work, as described in my patent application, deletions within the 3'-5' exonuclease domain can destroy polymerase activity. Thus, the description in the '155 patent regarding the 3'-'5 exonuclease domain is wrong.

3. The first correct mutant sequences disclosed by the Chatterjee group appear in the specification that led to the issuance U.S. Pat. No. 5,939,301 ("the '301 patent"), filed October 2, 1995. Prior to the filing of the '301 patent, and after the filing of our own patent application, my research group presented our findings at scientific meeting through a poster presentation. The presentation included the full sequence of the *Thermotoga neapolitana* polymerase and the location of 5' exonuclease and 3'-5' exonuclease mutants that are described in our patent application. The poster was visited by members of the Life Technologies Corporation, who took notes. The '301 patent was filed shortly thereafter, including correct mutant sequences, at least one of which, a Asp to Ala substitution at position 323, is identical to a 3'-5' exonuclease mutant disclosed in our poster presentation and in our patent application.

4. I further declare that all statements made herein are of my own knowledge, are true, and that all statements are made on information and belief that are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 Title 18 of the United States

Code, and that such willful statements may jeopardize the validity of the application of any patent issued thereon.

Dated: August 3, 2004

Michael Slater